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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/031,371	04/30/2002	Maria Cristina Geroni	217550US0PCT	2516

22850 7590 12/03/2002

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EXAMINER	
KRISHNAN, GANAPATHY	
ART UNIT	**PAPER NUMBER**
1623	6

DATE MAILED: 12/03/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/031,371	GERONI ET AL.	
	Examiner	Art Unit	
	Ganapathy Krishnan	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-8 and 12-16* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8 and 12-16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

On page 1 of the preliminary amendment filed on April 30, 2002, the applicants have canceled claims 9-11. However, in the same amendment, on page 3, it is stated that claims 1-9 and 12-16 are active. Since claim 9 has been cancelled, it should be restated that claims 1-8 and 12-16 are pending in the application. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 15 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the treatment of treatment of metastasis, does not reasonably provide enablement for the prevention of metastasis or the use of antimetabolites broadly. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with the claim.

A conclusion of lack of enablement means that, based on the evidence regarding each of the factors below, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation.

(A) The breadth of the claims
(B) The state of the prior art
(C) The level of one of ordinary skill
(D) The level of predictability in the art

(E) The amount of direction provided by the inventor
(F) The existence of working examples
(G) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

The breadth of the claims

Claim 15 is drawn to a method for prevention of metastasis in a mammal, including human, in need thereof, comprising administering the alkylating anthracycline of formula Ia or Ib as claimed in claim 1 and an antimetabolite in a synergistic antineoplastic amount. The scope of the claim is seen to include the administration of the said compounds and the inhibitor to a healthy mammal, and subsequent exposure to conditions that would cause metastasis, wherein the said compounds prevent said exposure from manifesting itself in said mammal so exposed.

The state of the prior art

The examiner notes that the art cited by the applicants mention methods of treatment of tumors and cancers. However, there is no disclosure of potential metastasis preventive activity of compounds seen in the prior art. The prior art appears to be silent with regard to preventive procedures recognized by skilled artisans in the field.

The level of one of ordinary skill

The skilled artisan in this field is that of an MD for chemotherapeutic administration and/or a Ph.D. skilled in the development of chemotherapeutics.

The level of predictability in the art

The examiner acknowledges the probability and predictability that administration of the said compounds would have a reasonable expectation of success for preventing metastasis. There

is not seen sufficient data to substantiate the assertion that metastasis may be prevented by the use of the compounds instantly claimed.

The amount of direction provided by the inventor

The instant specification is not seen to provide enough guidance that would allow a skilled artisan to extrapolate from the disclosure and the examples provided to enable the use of the active agents to prevent metastasis. The specification also fails to direct the skilled artisan in correlative prior art procedures which might provide the basis for an advance in treating tumor which induces prevention of the said disease.

The existence of working examples

The working examples set forth in the instant specification are drawn to data involving murine L1210 cells. The skilled artisan in this field would not extrapolate the preventive efficacy of the compounds claimed or the use of the same in preventive methods from just this example provided. The disclosure does not show the prevention of metastasis. However, it is seen to show the antileukemic effect of the active agents.

The quantity of experimentation needed to make or use the invention based on the content of the disclosure

Indeed, in view of the information set forth, the instant disclosure is not seen to be sufficient to enable the prevention of metastasis with the compounds set forth in the claims. A skilled artisan would not extrapolate the preventive efficacy from the results disclosed for the examples in murine L1210 cells, set forth in the instant specifications.

Claims 3, 4 and 6 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for gemcitabine, does not reasonably provide enablement for cytidine analogs, 5-fluoropyrimidine and 5-fluorouracil. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-6 and 12-16 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 recites a product containing an alkylating agent of formula Ia or Ib and an antimetabolite as a combined preparation for simultaneous, separate or sequential use in the treatment of tumors. It is not clear how the product containing the alkylating agent and the antimetabolite as a combined preparation can be used separately or sequentially. This renders the claim indefinite.

Claims 2-6 are also rendered indefinite since they are dependent on a base claim which is indefinite.

A broad range or limitation together with a narrow range or limitation that falls within the broad range or limitation (in the same claim) is considered indefinite, since the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. Note the explanation given by the Board of Patent Appeals and Interferences in *Ex parte Wu*, 10

USPQ2d 2031, 2033 (Bd. Pat. App. & Inter. 1989), as to where broad language is followed by "such as" and then narrow language. The Board stated that this can render a claim indefinite by raising a question or doubt as to whether the feature introduced by such language is (a) merely exemplary of the remainder of the claim, and therefore not required, or (b) a required feature of the claims. Note also, for example, the decisions of *Ex parte Steigewald*, 131 USPQ 74 (Bd. App. 1961); *Ex parte Hall*, 83 USPQ 38 (Bd. App. 1948); and *Ex parte Hasche*, 86 USPQ 481 (Bd. App. 1949). In the present instance, claims 12-16 recite the broad recitation mammal, and the claim also recites human, which is the narrower statement of the range/limitation.

Joint Inventors

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person

> having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Marchini et al (Anti-Cancer Drug Design, 1995, 10, 641-653) in combination with Suarato et al (Anthracycline Antibiotics, 1995, 142-155), Elslager et al (USPN 4,853,221), Viale et al (Anti-Cancer Drugs, 1998, 9, 457-463), Koeffler et al (Cancer, 1981, 48, 1958-63) and Hertel et al (Cancer Research, 1990, vol. 50, pp 4417-4422)

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1-8 are drawn to a product containing an alkylating anthracycline of formula Ia or Ib and an antimetabolite compound for treatment of tumors; wherein the antimetabolite compound is 5-fluorouracil and gemcitabine and a pharmaceutical composition containing the compounds of formula Ia or Ib and 5-fluoruracil or gemcitabine.

Marchini et al teach the cytotoxic effects of compounds Ia and Ib in murine leukemia cell line L1210 (see page 642, line 11 to page 645, line 2 and Table I, page 645). The compounds were also used as a composition by dissolution in sterile water (see page 642, first and second paragraphs under the subheading Materials and methods).

Suarato et al is drawn to anthracyclines with modifications at the C-3' position of the sugar moiety and their activity on multidrug resistant tumor cells. This reference also discloses

the antitumor activity of compound Ib against leukemias (see page 152,last paragraph through page 153).

But Marchini and Suarato et al do not teach the use of the compounds Ia and Ib with an antimetabolite as a combined preparation in a synergistic antineoplastic amount for treatment of tumors

Elslager et al drawn to a method for treatment of non-small cell lung cancer, head and neck and breast cancers, discloses the use of 5-fluorouracil in the palliative management of carcinoma (see col. 2, lines 43-48). Elslager also discloses that the combination regimen of 5-fluorouracil with an additional active agent was superior to 5-fluorouracil alone against tumor cell lines (see col. 9, lines 43-49).

Viale et al drawn to a method of treatment of cancer, also disclose the synergism of 5-fluorouracil with an art recognized anticancer agent to treat ovarian cancer cell lines. 5-fluorouracil was chosen as one of the antimetabolites since it is commonly used in clinical testing (see page 457, abstract).

Koeffler et al drawn to leukemia chemotherapy, disclose the use of the antimetabolite 5-azacytidine, which is an analog of cytidine, as a chemotherapeutic agent of choice for treatment of acute myelogenous leukemia (see page 1962, second full paragraph).

Hefler et al drawn to the antitumor activity of gemcitabine, disclose that it is a very potent antimetabolite with a broad spectrum antitumor activity and inhibited the growth of human leukemia cells at 1ng/ml concentration (see abstract and page 4420, right column, under Discussion, paragraphs 1-3).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to combine compounds Ia or Ib with antimetabolites 5-fluorouracil and gemcitabine to make a product and compositions for treatment of tumors, with a reasonable expectation of success. The idea of combining them flows logically from their having been individually taught in prior art for the treatment of cancers and tumors. The examiner rejects the compositions set forth as products or compositions, when the components are used separately or sequentially. It is unclear how these products are a combined preparation, but utilizable separately.

One of ordinary skill in the art would be motivated to do so since the prior art teaches the desirability to use 5-fluorouracil in combination with other anticancer agents. The synergistic effects and the ability to use less of a toxic anticancer agent co-administered with 5-fluorouracil and gemcitabine provides sufficient motivation to use combinations of these two antimetabolites with compounds of formula Ia or Ib for making products and compositions.

Claims 12-16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Marchini et al (Anti-Cancer Drug Design, 1995, 10, 641-653) in combination with Suarato et al (Anthracycline Antibiotics, 1995, 142-155), Elslager et al (USPN 4,853,221), Viale et al (Anti-Cancer Drugs, 1998, 9, 457-463), Koeffler et al (Cancer, 1981, 48, 1958-63) and Hertel et al (Cancer Research, 1990, vol. 50, pp 4417-4422).

Claims 12-16 are drawn to methods of treating tumors, metastasis and treating tumor by inhibition of angiogenesis by administering compounds of formula Ia or Ib and an antimetabolite compound in a synergistic antineoplastic amount.

Marchini et al teach the cytotoxic effects of compounds Ia and Ib in murine leukemia cell line L1210 (see page 642, line 11 to page 645, line 2 and Table I, page 645). The compounds were also dissolved in sterile water immediately before use (see page 642, first and second paragraphs under the subheading Materials and methods)

Suarato et al is drawn to anthracyclines with modifications at the C-3' position of the sugar moiety and their activity on multidrug resistant tumor cells. This reference also discloses the antitumor activity of compound Ib against leukemias (see page 152,last paragraph through page 153).

But Marchini and Suarato et al do not teach the use of the compounds Ia or Ib with an antimetabolite as a combined preparation in a synergistic antineoplastic amount in a method for treatment of tumors

Elslager et al drawn to a method for treatment of non-small cell lung cancer, head and neck and breast cancers, discloses the use of 5-fluorouracil in the palliative management of carcinoma (see col. 2, lines 43-48). Elslager also discloses that the combination regimen of 5-fluorouracil with an additional active agent was superior to 5-fluorouracil alone against tumor cell lines (see col. 9, lines 43-49).

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Koeffler et al drawn to leukemia chemotherapy, disclose the use of the antimetabolite 5-azacytidine, which is an analog of cytidine, as a chemotherapeutic agent of choice for treatment of acute myelogenous leukemia (see page 1962, second full paragraph).

Hefler et al drawn to the antitumor activity of gemcitabine, disclose that it is a very potent antimetabolite with a broad spectrum antitumor activity and inhibited the growth of human leukemia cells at 1ng/ml concentration (see abstract and page 4420, right column, under Discussion, paragraphs 1-3).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of the prior art cited above and come up with a method of treating tumors and cancers using a combination of the compounds of formula Ia or Ib with 5-fluorouracil and gemcitabine, with a reasonable expectation of success. The idea of combining them flows logically from their having been individually taught in prior art for the treatment of cancers and tumors. Additionally, the prior art teaches the desirability to use the compound 5-fluorouracil in combination with other anti-cancer agents. The synergistic effects and the ability to use less of a toxic anticancer agent co-administered with 5-fluorouracil provides sufficient motivation to use combinations of anticancer drugs in methods for treating cancer.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ganapathy Krishnan whose telephone number is 703-305-4837. The examiner can normally be reached on 8.30am-5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James O. Wilson can be reached on 703-308-4624. The fax phone numbers for the

organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1235.

GK
December 1, 2002

JAMES O. WILSON
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600